Safety and the JAK inhibitors: How Did the FDA Make Their Decisions?

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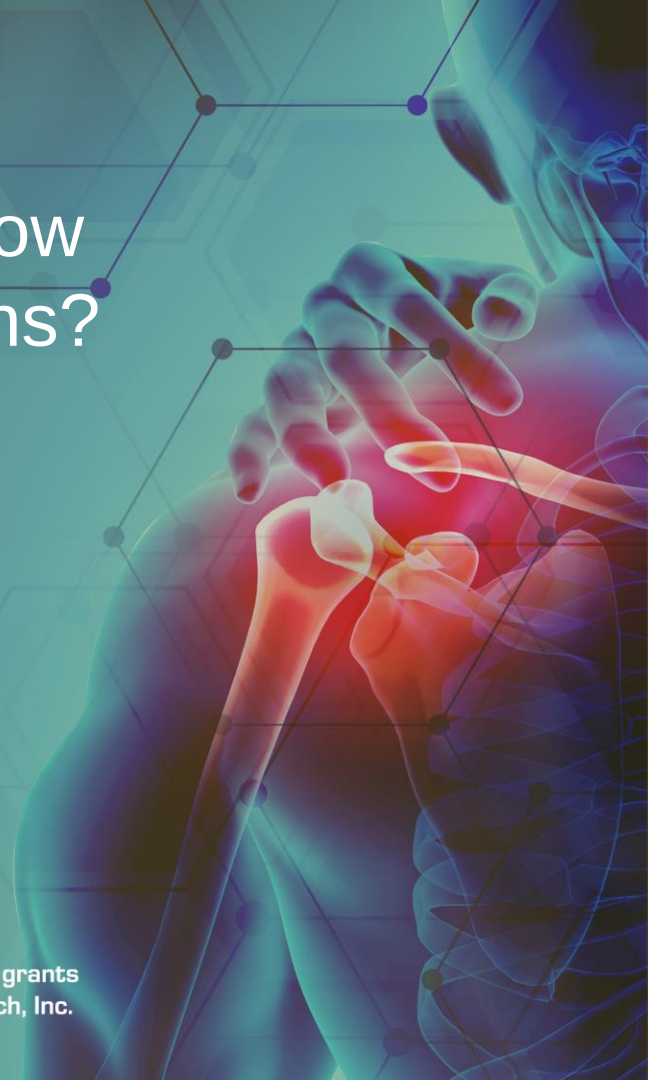

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FDA Updates at ACR2021

- **New**
  - V
  - A
  - A
- **New**
  - B
  - A
  - T
  - Rilonacept for recurrent pericarditis, 03/18/2021
  - Immune Globulin Intravenous, Human 10% for DM, 07/15/2021
- **Other approval:**
  - Rituximab-arrx: 12/17/2020

- **Safety of JAK Inhibitors for Inflammatory Conditions:**
  - MACE, malignancies, thrombosis, and mortality
  - Revisions to Warnings, including Boxed Warning*
  - Revisions to Indications*
- **Safety of Collagenase Clostridium Histolyticum:**
  - Serious injury to the injected finger/hand in the treatment of Dupuytren's contracture
- **Safety of NSAIDs:**
  - Fetal renal dysfunction, oligohydramnios, neonatal renal impairment
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

FDA Presentation at ACR2021.

Historically FDA Division: Pulmonary, Allergy, Rheumatology [DPARP]

- Has been the most conservative review Division at FDA CDER
- After CDER reorganization in 2003 this Division assumed review of “therapeutic biologics” from CBER:
  - Monoclonal antibodies [mAbs]
  - Proteins for therapeutic use: cytokines, enzymes, thrombolytics but NOT vaccines nor blood products
  - Immunomodulators
  - Growth factors, cytokines, mAbs intended to mobilize, stimulate, alter production of hematopoietic stem cells
- Remaining in CBER:
  - Cellular products → Regenerative Medicine Advanced Therapeutics [RMAT]
  - Gene Therapy
  - Vaccines
  - Allergenic extracts, anti-venins, venoms
  - Blood products

FDA Division: Pulmonary, Allergy, Rheumatology [DPARP], Now Rheumatology –Transplant Medicine [DRTM]

- DAAODP: Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products; Lee Simon MD, a Rheumatologist, was Director: 2001 □ 2003
- In 2010, DAARP became DAAAP and DPARP
  - Rheumatology moved to Pulmonary and Allergy
  - Ophthalmology becomes its own Division
  - DAAAP: Division of Anesthesia, Anti-Inflammatory, Addiction and Pain Medicine regulates and reviews Investigational New Drug (IND) applications and marketing applications for drug and biologic products for the treatment of Acute Pain and Chronic pain [including OA]
- In 2020: DPARP moved to the Office of Immunology and Inflammation as DRTM
  - Division of Pulmonology, Allergy and Critical Care (DPACC), also in Office of Imm/Inflammation
  - Badrul Chowdhury MD, Allergist, was Director, DPARP and left FDA in 2018
  - Nikolay Nikolov, a Rheumatologist, 'trained under' Chowdhury and had been Acting Division Director
  - Nokolov assumed Directorship of DRTM September 2020; Acting Director March 2020
  - DAAAP became Division of Anesthesiology, Addiction and Pain Medicine (DAAPM) in Office of Neuroscience; still regulates OA, NSAIDs/topicals

Historical Safety Issues in Rheumatology: NSAIDs and COX-2s

- Benoxaprofen [Oraflex]: voluntary withdrawal by Lilly on Aug 4, 1982 due to liver toxicity
  - Initial approval April 18, 1982
- Rofecoxib [Vioxx]: voluntary withdrawal by Merck in 2004: 140,000 MIs during 5 years on US market
- Valdecoxib [Bextra]: voluntary withdrawal by Pfizer in 2005: FDA stated: CV, GI and skin related AEs
- Celecoxib: PRECISION safety study: n=24,081, published 2016 [1]
  - Risk of death, CVA or MI among patients taking celecoxib 2.3% during a 30-month period, compared with 2.5% with naproxen and 2.7% with ibuprofen
  - Risk of GI events significantly lower with celecoxib than naproxen (p=0.01) or ibuprofen (p=0.002);
  - Risk of renal events significantly lower with celecoxib than ibuprofen (p=0.004)
- April 24-25, 2018: FDA AAC and Drug Safety and Risk Committees: vote 15 - 5 to update Celebrex label
- 2018: FDA strengthens warning that NSAIDs increase MI and CVA risks
  - Even w/ short term use; risks may begin within weeks of starting a dose
  - Risks increase with increasing doses; especially in those w/ CV risks
  - “Use at lowest dose possible for shortest period of time”

Nissen SE et al. *NEJM*. 2016: 2159-2529.

FDA Assessment of Benefit-Risk: Draft Briefing Document: Sept 2021

- The US Food and Drug Administration (FDA) is required to consider whether a product is “safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.”
- According to the recently released [Sept 2021] draft guidance:
  “In certain circumstances, such as in the review of drugs to diagnose and treat communicable diseases or drugs identified as controlled substances, FDA’s benefit-risk assessment incorporates broader public health considerations for both the target patient population and others, such as risks related to misuse, accidental exposure, or disease transmission.”
  - Opoids
  - Antimicrobial resistance
  - Vaccines
- Reflects FDA thinking over the past several years coincident w/ COVID

https://www.fda.gov/media/152544/download.

FDA's Benefit-Risk Framework for New "Therapy" Review

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Context of use Relevance of condition to intended population Public health implications	
Current Treatment Options	Current Rx; Standard of care Other interventions; off label use Medical Need	
Benefit	Strength of trials; endpoints Clinical relevance of benefit: nature of effect; effect size; distribution of benefit Time course, durability; subpopulations; generalizability; use of therapy	
Risk and Risk Management	Strengths, limitations of evidence; observed safety signals & importance Causal association; strength of evidence; impact of product quality Potential for misuse, accidental exposure	
Conclusions Regarding Benefit-Risk Overall conclusions; relative importance; time course Ability of pts & HCPs to assess benefits; monitor safety; Adequate communication; boxed warnings, REMS, postmarketing safety study		

Recent FDA Assessment of Benefit-Risk: Avacopan in ANCA Assoc Vasculitis (AAV)

- July 9, 2020: Chemocentryx submits NDA for oral C5a inhibitor for treatment of AAV
  - Granted orphan indication; based on Ph 3 RCT comparing Avacopan vs Placebo added to SOC, defined as either RTX or CTX induction followed by AZA maintenance; including Prednisone tapering; administration w/ RTX and brief 2 week increases for [impending] flares
- May 6, 2021: FDA AAC Meeting:
  - Questions: single phase 3 RCT; description as Avacopan vs Prednisolone SOC
  - Criticisms: prednisone use; protocol allowed vs GCs for flares; total 1349 vs 3655mg GC doses
  - Criticisms: RTX maintenance not approved at time of protocol approval;

    More pts rec'd RTX induction and better responses in these pts
  - FDA: concerns re liver toxicity; response: pts receiving multiple medications; none experienced increases after initiating avacopan
  - VOTE: Efficacy: 9 YES; 9 No; Safety: 10 YES; 8 No; Benefit/Risk: 10 YES; 8 No
- July 6, 2021: Chemocentryx files NDA Amendment to respond to FDA questions/concerns
- October 8, 2021: Avacopan conditionally approved as: "adjunctive treatment of adult patients with severe active AAV in combination with standard therapy including GCs", with the caution that it:
  - "Does not eliminate glucocorticoid use"; and extensive post-marketing commitments

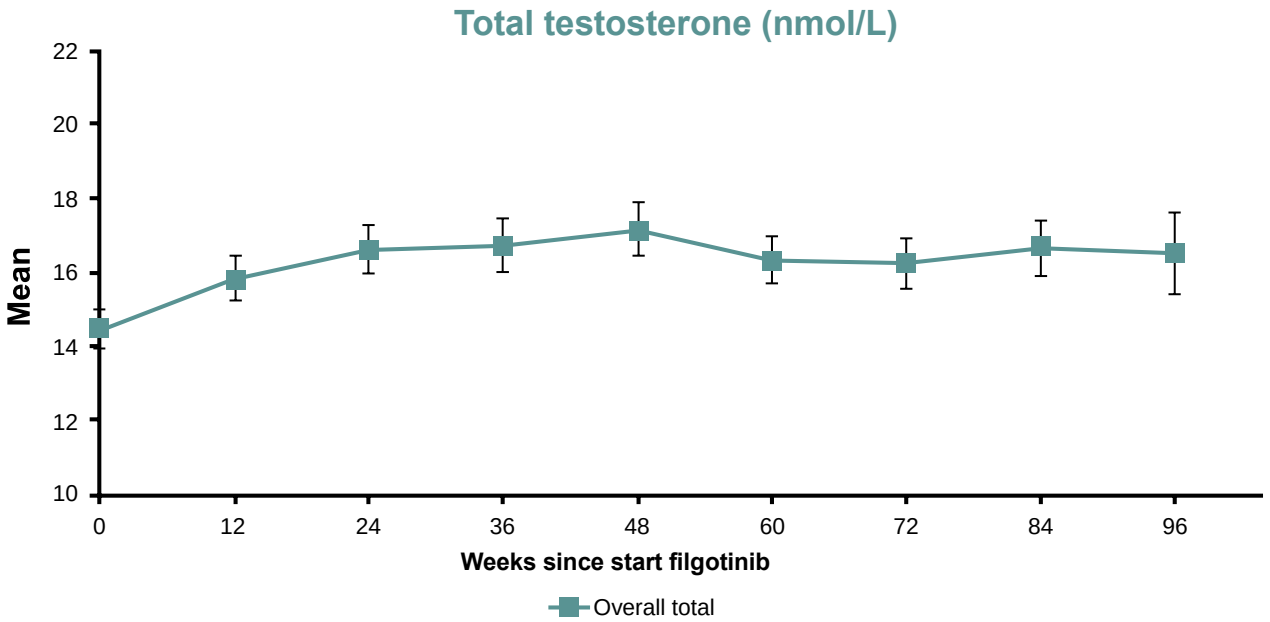
Evolution of the Safety Profile of the JAK Inhibitors and FDA Opinions Regarding Their Use

Filgotinib: A Special Case: Testicular Toxicity?

- Preclinical: male reproductive organs affected in all species studied; male beagle dogs most sensitive
- Preclinical murine fertility findings vs other JAKis:
  - FIL: 2 wk repeated dose toxicity study rodents: tubular atrophy and luminal cell debris observed in testis and epididymis
  - TOFA: exposure equivalent to 5 & 10mg doses no impairment of fertility
    - 133x dose NE male fertility, sperm conc or motility
    - 17x dose increased post implantation loss
  - BARI: doses 113 and 169x MHRD [max human recommended dose]: reproductive performance unaffected, but fertility reduced in male & female rats
    - 25x and 48x MHRD maintenance of pregnancy adversely affected
    - Increased implantation losses; decreased number of viable embryos
  - UPA: dose 2x MHRD number viable embryos unaffected in females mated to males also dosed
    - 42x and 84x MHRD NE on fertility
    - Doses of 25 and 75 mg/kg/day maintenance of pregnancy adversely affected

XELJANZ US PI; OLUMIANT US PI; RINVOQ US PI.

Filgotinib: A Special Case: Testicular Toxicity?



Normal ranges (nmol/L) in males
≥18y: 8.40–28.70 nmol/L

- Integrated analysis of adult male patients w/ active RA from Ph 2 DARWIN 1, 2, 3 trials of filgotinib, testosterone levels were stable and within normal ranges over time

1. Ki S et al. *Arthritis Rheumatol*. 2019; 71 (suppl 10). Abstract 992; 2. Galapagos. *Investor Relations*. Accessed September, 2020.

Filgotinib: A Special Case: Testicular Toxicity?

MANTA-RAy

International, randomized, double-blind (DB), PBO-controlled Phase 2 Rheumatology study assessing the impact of filgotinib on sperm parameters[1]

- **Key inclusion criteria:**
  - Male age 21–65
  - Diagnosis: RA, PsA, AS, or nr-axSpA ≥ 12 weeks prior to screening
- **Key exclusion criteria:**
  - Previous male reproductive health problems
  - Prior diagnosis of male infertility
  - Use of concomitant prohibited medications as outlined by protocol
- **Study Duration:** study includes a 13-week DB phase and an extension phase lasting up to 156 weeks
- **Treatment:** patients received 200 mg filgotinib oral QD or PBO in the form of an oral tablet QD
- **Primary endpoint:** proportion of participants with a ≥ 50% decrease from baseline in sperm concentration at Week 13

MANTA study is similar but includes patients with IBD[2]

- Both studies are fully recruited with topline results anticipated in the first half of 2021[3]

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03926195. Accessed September 15, 2020;
3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03201445. Accessed September 15, 2020.

Filgotinib: FDA Complete Response Letter

- **Filgotinib NDA** for treatment of ”moderate to severely active RA”
- FDA requested data from MANTA and MANTA-RAy studies (assessing the impact of filgotinib on sperm parameters) before completing review of NDA
- FDA expressed concerns regarding the overall benefit/risk profile of the Filgotinib 200mg dose
- Filgotinib recently received a positive opinion from the EMA's Committee for Medicinal Products for Human Use, recommending marketing authorization for filgotinib in the EU for the treatment of adults with moderate to severe RA who have responded inadequately or are intolerant of ≥1 DMARDs
- August 18, 2020: **FDA DRTM releases Complete Response Letter re Filgotinib**
  - Had requested full review of MANTA and MANTA-RAy studies re impact of Filgotinib on sperm parameters before completing review of NDA; anticipated completion 2021
  - Also expressed concerns regarding overall benefit/risk profile of 200mg dose
- Galapagos CEO predicts that "there is a good chance" that filgotinib will eventually launch in the US; however, it is currently "difficult to estimate whether we can launch filgotinib [in US] at a dose of 200 milligrams”

1. Gilead press release. https://www.gilead.com/news-and-press/press-room/press-releases/2020/8/gilead-receives-complete-response-letter-for-filgotinib-for-the-treatment-of-moderately-to-severely-active-rheumatoid-arthritis. Accessed August 19, 2020.
2. Archyde. https://www.archyde.com/galapagos-ceo-this-is-very-sour/ Accessed August 28, 2020;
3. https://www.ema.europa.eu/en/documents/assessment-report/jyseleca-epar-public-assessment-report_en.pdf Accessed January 27, 2022.

The “Evolution” of the Safety Profile of JAKis…

- May 9, 2012: **Tofacitinib** FDA Arthritis Advisory Committee (AAC) meeting:
  - Concerns re safety profile of 10mg BID: malignancies and MACEs; esp as exposure to higher dose more limited; Resulted in commitment for post-marketing safety trial
  - VOTES: Efficacy: YES: 10; Safety: YES: 7; No: 2; Benefit/Risk: YES: 8; No: 2
- November 6, 2012: **Tofacitinib** NDA approved
- January 14, 2016: **Baricitinib** NDA submitted: indication: “moderate to severely active RA”
  - Complete Response Letter on April 12, 2017
  - An imbalance in thrombotic events in the baricitinib RA program with potential thrombotic risk with use of baricitinib in RA; inadequate safety exposure for 2 mg of baricitinib
  - Not consistent findings to conclude greater efficacy with 4 mg over 2 mg
  - Lower doses of Baricitinib should be considered for use in RA as there was evidence that lower doses may be effective for treatment of RA
- December 04, 2017: **Baricitinib** NDA re-submission: “moderate to severely active RA: MTX intolerant or MTX-IR”
  - Proposed dose 2mg QD
  - Updated analyses of accumulated safety (cut-off date, April 01, 2017 vs. August 01, 2015)
  - Epidemiological data comparing rates of VTE/PE from retrospective cohorts to RCT data

Baricitinib: FDA Arthritis Advisory Committee Mtg 4/23/2018

- April 23, 2018: **Baricitinib** RA NDA: FDA AAC meeting review: excess of VTEs in 4mg dose
  - Tofacitinib: no increase in VTEs in clinical development program in RA
  - Upacitinib: increased incidence VTEs in phase 2 but NOT phase 3 RCTs
- FDA AAC Committee Meeting votes to approve **Baricitinib** 2mg but NOT 4mg dose
  - Insufficient data to support 4mg for pts failing multiple DMARDs, eg 'refractory'
  - Clear signal of VTEs w/ 4mg – not sufficient safety
  - Votes: 2mg: efficacy: YES: 14; No: 1; Safety: YES: 9; No: 6; Benefit/Risk: YES: 10; No: 5

    4mg: 15 0 5 10 5 10
- March 19, 2018: **Baricitinib** NDA approved
  - Only 2mg QD dose approved; ONLY in RA patients who are TNF-IR
  - Data included in label from only 2 of 4 confirmatory ph 3 RCTs; only placebo and 2mg
  - Commitment for post marketing safety study: 2 doses Bari; active comparator to evaluate VTEs, MACEs, OIs, malignancies
  - Black Box Warning: SIEs, lymphoma & malignancies and VTEs/ATEs

The “Evolution” of the Safety Profile of JAKis…

- August 16, 2019: **Upadacitinib** NDA in RA approved
  - No FDA AAC Meeting Review
  - Abbvie agrees to accept Black Box Warnings for: SIEs, Lymphoma & malignancies and VTEs, based on Baricitinib & Tofacitinib labels
- December 6, 2021: **Baricitinib** label updated
  - Black Box warning updated to include: Mortality and MACEs based on ORAL Surveillance postmarketing safety study
  - Use in RA has always been limited to patients failing TNFis
- December 14, 2021: **Upadacitinib** label updated
  - Psoriatic Arthritis added as indication
  - Black Box warning updated to include: Mortality; Malignancies, MACEs and VTES, based on ORAL Surveillance postmarketing safety study
  - Use in RA limited to patients failing TNFis
- January 24, 2022: **Upadacitinib** label updated
  - Atopic Dermatitis added as indication
  - Label updated to include: Hypersensitivity Rxns and Embryo-Fetal Toxicity

A Relevant Example of an FDA-Mandated Post Marketing Safety Trial

- A Previous Post Marketing Safety Trial Commitment:
  ENTRACTE RCT: TCZ vs ETN: Major Adverse CV Events [MACEs]
- 3080 csDMARD-IR RA pts; ≥1 CV risk factor; randomized 1:1 TCZ 8 mg/kg/ IV q4w v ETN 50mg SQ qw
  - Open label; mean F/U 3.2 yrs; drop-outs 4%
  - 1° EP: time to 1st occurrence MACE; powered to exclude HR of MACE ≥ 1.8 w/ TCZ vs ETN
    - TCZ: 83 vs ETN: 78 MACEs; HR: 1.05 (95% confidence interval 0.77–1.43)
    - Ruled out a risk for occurrence of MACEs ≥ 1.43 w/ TCZ
    - SIEs and GI perforations more frequent w/ TCZ
    - Elevated LDL, HDL, total cholesterol and TGs w/ TCZ
- Published 2020; FDA recommended same statistical non-inferiority margins as for ENTRACTE; yet data had not been released or published

Giles JT et al. *A+R*. 2020; 72:31-40.

Timeline: “Reveals” From ORAL Surveillance RCT

- 2/19/19: PFI press release: Transition of pts receiving Tofa 10mg in trial to 5mg BID
  - In response to DSMB: increase in frequency of PEs and overall mortality in pts receiving 10mg BID
- 2/25/19: FDA announcement: actively examining and working w/ PFI to better understand data; still believes benefits outweigh risks
- 3/20/19: EMA notification: increased risk of PEs & death
- 5/17/19: EMA Pharmacovigilance Risk Assessment Committee [PRAC] recommends Tofa 10mg BID dose not be prescribed to pts at high risk for PEs
- 7/26/19: FDA adds new boxed warning to Tofa label for PEs & DVTs (VTEs) w/ 10mg dose
- 11/16/19: EMA confirms PRAC recommendations:
  - Tofa to be used w/ caution in pts at high risk for VTEs;
  - Maintenance dose of 10mg not be used in UC pts at high risk unless no suitable alternative;
  - Due to increased risk SIEs, not be used in pts ≥65 years unless no alternative

Timeline: “Reveals” From ORAL Surveillance RCT

- 1/27/21: PFI press release: co-primary EPs: MACEs & malignancies did NOT meet co-primary EP of non-inferiority to TNFis
- 2/4/21: FDA issued Drug Safety Communication [DSC]: “HCPs should consider benefits & risks of Tofa when considering if patients should continue medication”
- 2/16/21: PFI: Important Drug Warning
- 6/11/21: EMA confirms PRAC mtg: “advising HCPs that Xeljanz should only be used in patients over 65 years of age, pts who are current or past smokers, … with other CV risk factors, and with other malignancy risk factors, if no suitable treatment alternative is available.”
- 7/6/21: EMA disseminates Direct Healthcare Professional Communication [DHPC] w/ detailed data summarizing IRs and HRs of MACEs & malignancies from Surveillance RCT
- 9/1/21: FDA announces required revisions to boxed warnings of all approved JAKis & RA pts fail a TNFi prior to receiving JAKi Rx
- 12/3/21: PFI announces FDA updated Black Box warning for use of Tofa
  - Black Box warning updated to include: Mortality; Malignancies, MACEs and VTES, based on ORAL Surveillance postmarketing safety study
  - Use in RA limited to those patients failing TNFis

ORAL Surveillance: Risk for MACEs & Malignancies: RA Pts ≥50 Yrs w/ ≥2 CV Risks

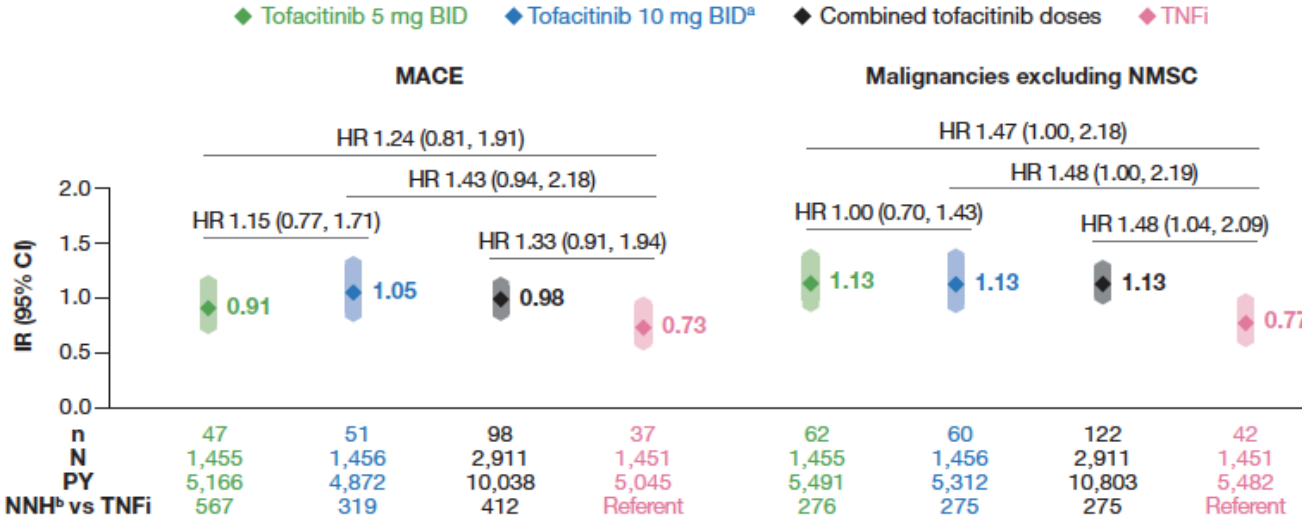
ACR Convergence 2021 Abstracts:

- **0831: ORAL Surveillance:** Overall Conclusions
- **0958:** MACEs
- **1940:** Malignancies excluding NMSC
- **1941:** VTEs
- **1684:** Infections
- **1939: STAR-RA:** MACEs
- **1675: STAR-RA:** Malignancies excluding NMSC

Oral Surveillance: Overview: Safety of Tofa v TNFi's in RA Pts ≥50 Yrs w ≥ 2 CV Risks

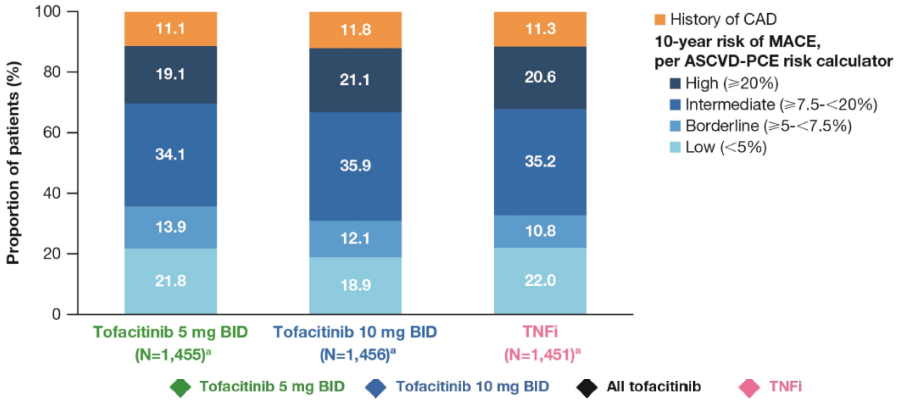
Open label Ph 3b/4 non-inferiority safety study in 4,362 RA pts; Criteria for non-inferiority NOT met

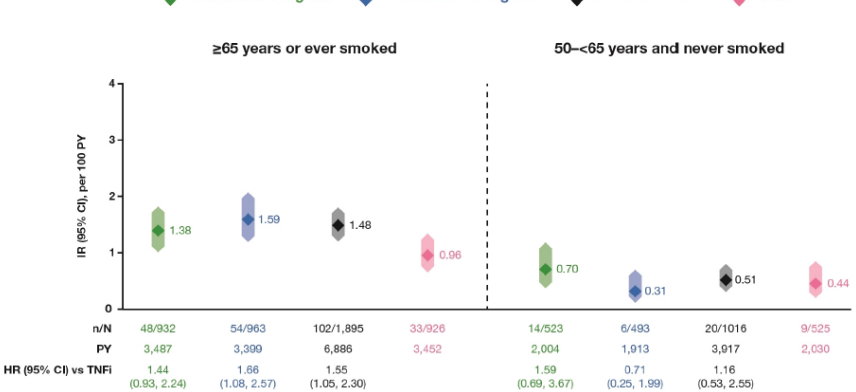
- In post hoc analyses, patients most at risk were aged ≥ 65 years or had ever smoked.
- IRs for MACE and malignancies <1.5 across all treatment groups, with overlapping 95% CIs
- Patient years (PY) exposure for tofacitinib 5 and 10 mg BID, respectively, for one addl event vs TNFis:
  - 567 and 319 PY for MACEs; NNH over 5 years vs TNFi: 113 and 64, respectively
  - 276 and 2



Ytterberg SR et al. *ACR*. 2021: #831.

Oral Surveillance: Risk Factors for MACEs and Malignancies [Excluding NMSC]

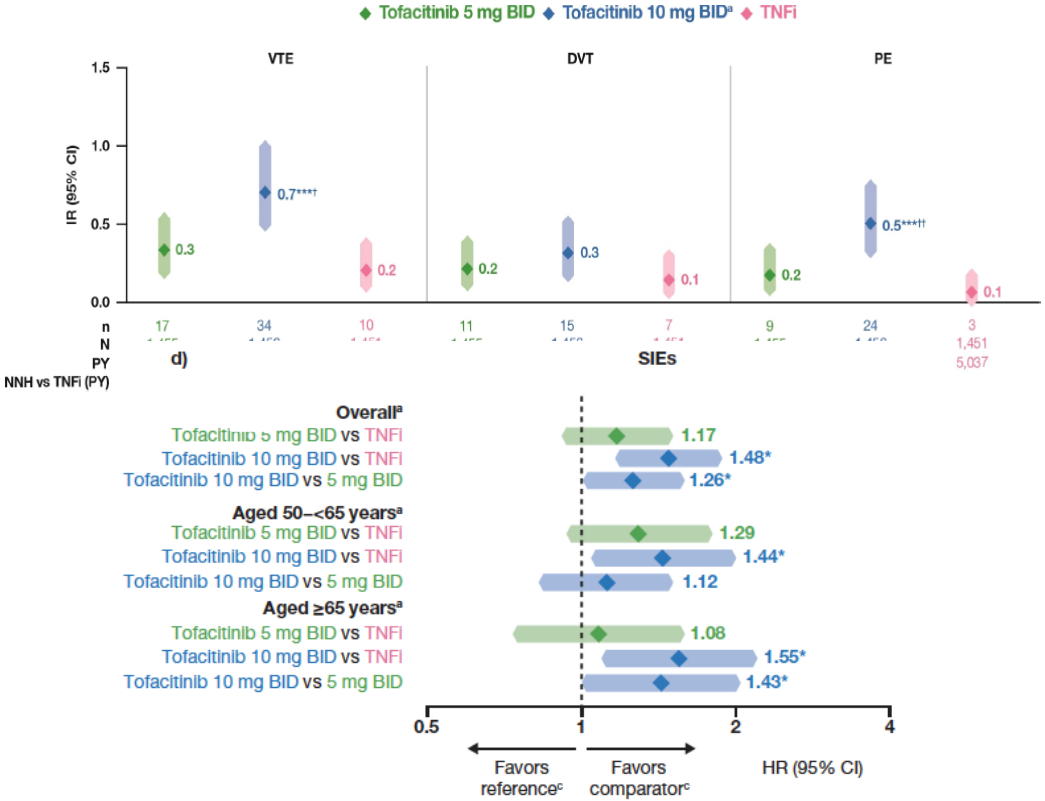




- Baseline covariates of current smoking, ASA use, age ≥ 65 yrs, male sex most significant risks for MACEs[1]
- MACEs and MIs specifically occurred in pts w/ Hx of CAD or at high risk for MACEs; less apparent w/ CVAs[1]
- Age [≥ 65 yrs] & ever smoking independent risk factors across all Rx groups for all malignancies excluding NMSC[2]
- Incidence ratios numerically higher for malignancies excl NMSC in North America[2]
- Effects of specific TNFi [ADA in No America] and ETN in RoW cannot be disentangled from regional differences in malignancy ascertainment[2]

1. Charles-Shoeman C et al. *ACR*. 2021: #958; 2. Curtis J et al. *Ibid*. #1940.

Oral Surveillance: Risk Factors for VTEs and Infections



- IRs for VTE, DVT and PE higher for Tofa 10 v 5mg BID v TNFi[1]
- Ad hoc safety analysis in 2019 led to dose reduction from Tofa 10 -> 5mg[1]
- Age, male sex, BMI ≥30kg/m^2; Hx HTN or VTE, use of GCs, HRT, anti-depressants[1]
- Incidence infex higher w/ Tofa v TNFi, specifically for H Zoster[2]
- IRs for all infex, HZ and SIEs higher in pts ≥ 65 yrs than those aged 50 - ≤65[2]
- HRs for SIEs numerically higher for Tofa 5mg v TNFi and 10 v 5mg Tofa; significantly higher for Tofa 10mg v TNFi and 10 v 5mg in pts ≥ 65 yrs[2]

1. Charles-Shoeman C et al. *ACR*. 2021: #1941; 2. Balenescu AR et al. *Ibid*. #1684.

STAR-RA: Safety of TofAcitinib in Routine Care Patients With Rheumatoid Arthritis

- Active comparator, new user design
- Data Sources:
  - Optum Clinformatics: Nov 2012 – June 2020
  - IBM MarketScan: Nov 2012 – Dec 2018
  - Medicare (Parts A, B, D): Nov 2012 – Dec 2017
- Real World Evidence (RWE): All RA patients Rxed routine care; F/U: CV outcome, switch, D/C, death RCT-duplicate: Inclusion and exclusion criteria of ORAL Surveillance trial
- 1° EP: Hospitalization for MI or CVA
- 2° EP: Individual CV endpoints, e.g.: MI, CVA, HF hospitalization, coronary revascularization
- Inclusion / Exclusion Criteria:
  - RA Pts Rxed w/ ≥ 365 days continuous enrollment prior to entry date; ≥ 2 RA Dx codes
  - New users w/ no prescription prior to cohort entry date; ≥ 1 script for MTX; ≥ 1 CV risk factor
  - No prior use of JAKi in TNFi users; no prior prescription of other JAKi in Tofa users
  - Pregnant or recently hospitalized w/ infections

1. Khosrow-Khavar F et a.ACR. 2021: #1939; 2. #1675.

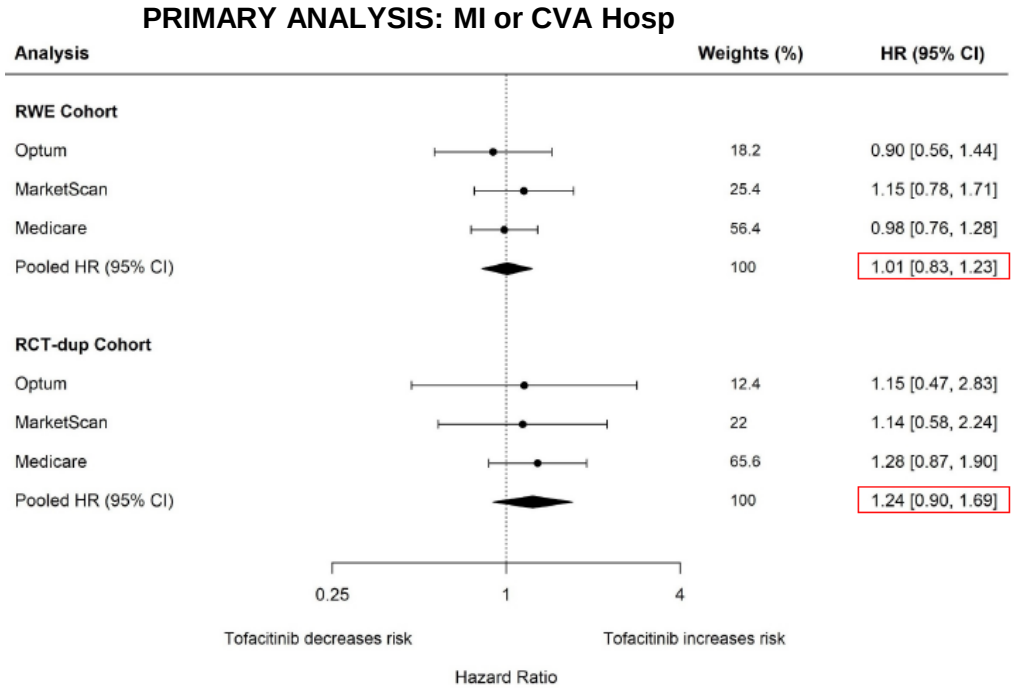
STAR-RA: Safety of TofAcitinib in Routine Care Patients With Rheumatoid Arthritis

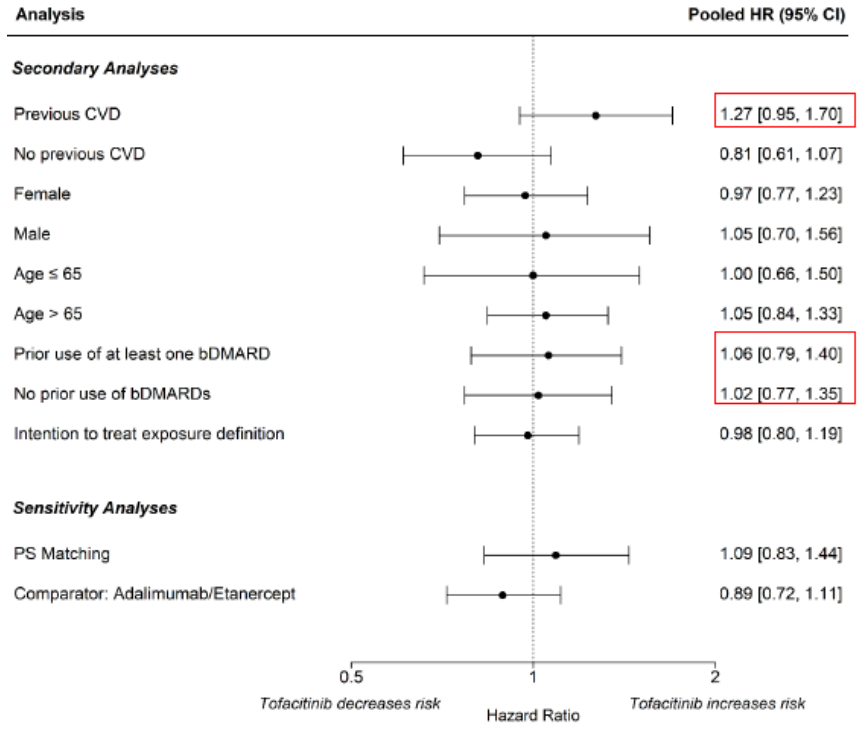
Statistical Analysis:

- Primary analysis: Cox proportional hazards model propensity score fine-stratification weighting
  - [1] Hospitalization for MI or CVA
  - [2] Any new malignancies excluding NMSC: 2 in or out-pt ICD-9 or -10 codes for same type of CA
- Secondary: ITT: maximum 365 days p Rx initiation
  - Subgroups: Age: ≤ 65 v >65; sex, bDMARDs rec'd: 0 v ≥1; Hx CVD
    - Sensitivity analyses: PS matching and ETN or ADA as comparator
- RWE Cohort: 102,263 RA pts: Optum: 28,568; MarketScan: 34,038; Medicare: 39,612
  - Tofa users: 12,852: 9.5 – 15.6% of users in each plan: 13.2, 15.6, 9.5%, respectively
  - Mean age: Tofa v TNFi: 57 v 55; 55 v 53, 72 v 72 years; 77 – 79% female; Hx CVD: 13, 10, 31%
  - csDMARD use: 75 – 81%; MTX: 54 – 62%; GCs: 69 – 72%; prior bDMARDs: 1.6 – 1.8 v 1.3 – 1.4
- Covariates: Demographics, lifestyle variables, RA related variables, comorbidities, co medications, markers of healthcare resource utilization, calendar year of cohort entry

1. Khosrow-Khavar F et al. *ACR*. 2021: #1939; 2. #1675.

STAR-RA: Safety of TofAcitinib in Routine Care Patients With Rheumatoid Arthritis





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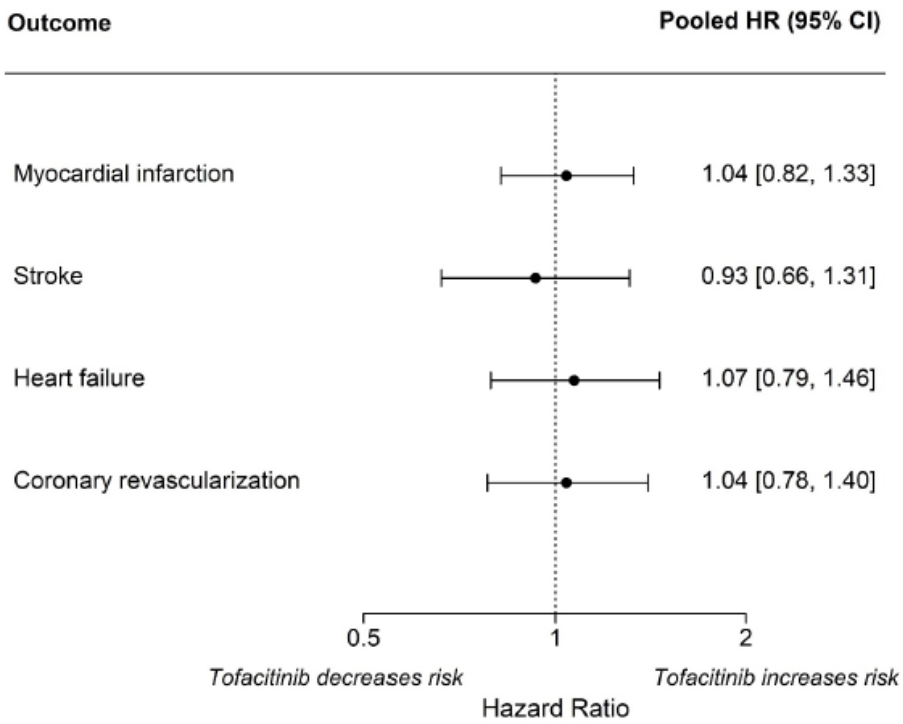

CONCLUSIONS:

- In this RWE study, Tofa, compared w/ TNFi, was NOT associated w/ increased risk of CV outcomes
- In patients w/ CV risk factors or Hx of CVD, an increased risk of CV outcomes w/ Tofa cannot be ruled out

1. Khosrow-Khavar F et al. ACR. 2021: #1939.

STAR-RA: Safety of TofAcitinib in Routine Care Patients With Rheumatoid Arthritis

Malignancies excluding NMSC:

- Primary Analysis:
  - Incidence rate (tofacitinib vs TNFI) per 100 person-years: 1.68 vs 1.36 in Optum, 0.60 vs 0.86 in MarketScan, 2.70 vs 2.49 in Medicare
  - RWE cohort, Pooled Hazard Ratio (95% CI): 1.01 (0.83, 1.22)
  - RCT-duplicate cohort, Pooled Hazard Ratio (95% CI): 1.17 (0.85, 1.62)
- Secondary Analysis: Real World Evidence (RWE Cohort):
  - Individual Cancer Endpoints (HR, 95% CI):
    - Lung Cancer: 1.20 (0.77, 1.87)
    - Breast Cancer: 0.85 (0.53, 1.38)
    - Prostate Cancer: 0.92 (0.51, 1.67)
    - Colorectal Cancer: 0.71 (0.33, 1.56)
    - Blood cancers: 0.91 (0.53, 1.58)
    - NMSC: 1.15 (0.96, 1.39)
  - Subgroup Analyses (HR, 95% CI):
    - Female: 0.93 (0.73, 1.18)
    - Male: 1.21 (0.86, 1.71)
    - Age ≤ 65: 0.89 (0.63, 1.24)
    - Age > 65: 1.08 (0.85, 1.37)
    - Previous bMARD: 0.81 (0.60, 1.10)
    - No previous bDMARD: 1.22 (0.96, 1.57)
- **CONCLUSIONS**: in this population based study, NO EVIDENCE of increased risk malignancies with Tofa. Increased risk of malignancies cannot be ruled out in older patients & with longer treatment duration.

Khosrow-Khavar F et al. ACR. 2021: #1675.